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Adverse drug reaction-related admissions in paediatrics, a prospective single-centre study

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ABSTRACT

Objective: To investigate the incidence and characteristics of hospital admissions related to adverse drug events in the paediatric setting.

Design: Prospective single-centre study.

Setting: A secondary and tertiary paediatric care centre.

Participants: A total of 683 acutely admitted patients, aged 0–18 year. All acutely admitted patients, using medication before admission, were prospectively screened for possible Adverse Drug Reactions (ADR)-related admission with a trigger list. Included cases were analysed with the Naranjo score for the assessment of causality.

Main outcome measures: This research explored the incidence of ADR-related admissions and investigated the relation between ADR and the licensing status of the medicines, as well as the severity and potential to prevent the ADRs.

Results: A total of 683 patients were admitted acutely during the study period, 47 of them were exposed to cancer chemotherapy. Fifteen patients not exposed to chemotherapy (2.4%) were admitted due to an ADR. Five of these 15 ADRs (33%) were caused by unlicensed or off-label used drugs. Thirty-two patients exposed to chemotherapy (68.1%) were admitted due to an ADR; 27 of these (84%) were caused by unlicensed or off-label used drugs.

Conclusions: In conclusion, this study shows that ADR-related hospital admissions occur more frequently in the paediatric population compared with adults, and more frequently in patients exposed to cancer chemotherapy. No relation was found between the unlicensed and off-label used drugs and the incidence of ADRs.

INTRODUCTION

Adverse Drug Events (ADEs) describe any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with this treatment.

ARTICLE SUMMARY

Article focus

- The aim of this research was to investigate the incidence and characteristics of hospital admissions related to adverse drug events in the paediatric setting.

Key messages

- Adverse Drug Reactions (ADR)-related hospital admissions occur more frequently in the paediatric population compared with adults.
- ADR-related hospital admissions occur more frequently in paediatric patients exposed to cancer chemotherapy.
- No relation was found between unlicensed and off-label use of drugs and the incidence of ADRs.

Strengths and limitations of the study

- A prospective study design was used.
- To our knowledge our study is the first on hospital admissions related to adverse drug events in the paediatric setting to be conducted in the Dutch setting.
- The number of patients included in this study was limited.
- The trigger list might have been incomplete.
- Data collection depended on information available in patient records.

Adverse Drug Reactions (ADRs) form a part of ADEs.¹ ADRs are defined as an unintended noxious response to a drug.² The definition of a medication error is any preventable event that may cause or lead to inappropriate medication use, or patient harm while the medication is in control of a healthcare professional, patient or consumer.² In the context of this study only the medication errors resulting in ADRs are taken into account.

Occurrence of ADRs is inherent to the use of medicines, and in some cases the severity of an event leads to hospital admission.

Adverse drug reaction-related admissions in paediatrics

However, most studies on hospital admissions related to medication use focus on adult patients.³ In adults ADE-related admissions form a great medical and economic burden, with a reported frequency in Dutch hospitals from 1.83% of all acute admissions including paediatric patients to 5.6% of all acute admitted adults.^{4 5} The burden in children seems to be lower, amounting up to 2.09%.⁶ Yet certain subgroups are at a greater risk, for example, in children exposed to cancer chemotherapy. Incidences of up to 22% have been reported.⁷

Risk factors for ADRs in children are relatively unknown. Pharmacodynamics and pharmacokinetics in children differ from adults and therefore the spectrum of adverse reactions in children may differ as well.⁸

Furthermore, children are more often exposed to unlicensed and off-label medication use, which potentially forms a greater risk for ADRs.^{9 10} Because part of these events may be preventable, more knowledge on occurrence and content of ADRs in the paediatric setting is necessary. The aim of this study was to prospectively investigate the incidence of ADRs as well as associated risk factors, such as licensing state, altered Pharmacokinetics and Pharmacodynamics (PK/PD)-behaviour or exposure to cancer chemotherapy in paediatric patients. Furthermore, severity of events as well as preventability was studied.

METHODS

This prospective study was performed in the Sophia Children's Hospital (SCH) in Rotterdam (the Netherlands) between March and July 2008. The SCH is a tertiary paediatric teaching hospital and is a major referral centre for paediatric patients within the South-western part of the Netherlands (about 4 million inhabitants).

Patients

All patients triaged at the emergency department and outpatient clinic of the SCH were considered for inclusion if they were acutely admitted to any of the clinical units of the SCH, or to paediatric wards of surrounding general hospitals, upon referral from the SCH.

Design

In order to determine the possibility of an ADR-related admission, all acutely admitted patients were assessed for the use of medication before admission. Patients admitted due to alcohol or drug abuse, a suicide attempt or admissions planned more than 24 h in advance were excluded from the study. Patients using medication were screened for a possible drug-related admission, based on a previously published trigger list.⁵ This trigger list was adapted for the paediatric setting by the use of an expert panel consisting of two paediatricians and three clinical pharmacists. Patients with a positive screening were included and analysed.

Included cases were assessed independently by a paediatrician and a pharmacist. Consensus was reached in a subsequent meeting. The likelihood of an ADR was

determined using the Naranjo score.¹¹ All patients with a Naranjo score of ≥ 1 (Naranjo score 'possible', 'likely' and 'certainly') were defined as cases and the licensing state of the drugs they used were identified. Medication registered for children at the Dutch Medicine Evaluation Board is called 'licensed' and medication that has not been registered for use in children is called 'unlicensed'. 'Off-label used medication' refers to drugs that are used outside the terms of the product license.¹² Furthermore, the degree of severity was scored prospectively based on the Le algorithm and the preventability was scored based on the Schumock algorithm.^{13 14}

Data were abstracted from patient records and included: date of birth, gender, reason for admission, number of admissions before current admission, comorbidity, medication used before admission (route of administration, form, dose, frequency and indication for use) and laboratory results during admission. When there was uncertainty about the information in the medical record extra-information for clarification was obtained from care providers involved.

Data from patients exposed to cancer chemotherapy were analysed separately, because these patients are expected to have a higher incidence of ADRs than the general paediatric population.

Analysis

Descriptive statistical methods were used for all end points.

RESULTS

A total number of 683 patients were admitted acutely to the SCH during the 18-week research period. In total, 264 patients were admitted for a symptom or sign corresponding with a symptom on the trigger-list and used medication before admission. Six patients admitted to the paediatric wards and intensive care unit (ICU) were excluded because of an autointoxication. The remaining 258 patients on the paediatric wards (211 patients) and ICU (47 patients) were included in the study. Forty-seven of these patients were exposed to cancer chemotherapy, and all were admitted to the medium care oncology department. Table 1 lists basic information on the acute admissions to the SCH and the patients included in this study.

Common infections, dyspnoea and convulsions were the most frequent reasons for admission to the paediatric wards and ICU. In the study population the most frequently used types of drugs before admission were, according to the Anatomical Therapeutic Chemical (ATC)/DDD index, classified as drugs for the alimentary tract and metabolism, the nervous system and anti-infectives for systemic use.¹⁵

For patients exposed to cancer chemotherapy the most frequent reason for admission was neutropenic fever. Besides antineoplastic and immunomodulating agents, most commonly used medicines for these

Adverse drug reaction-related admissions in paediatrics

Table 1 Acute admissions to the Sophia Children's Hospital

	Number of admissions	Patients included in the study
Acute admissions		
Total number of patients admitted	683	258
Patients admitted to the MCU	437	181
Patients admitted to the PICU	176	46
Patients admitted to the NICU	4	0
Patients admitted to other hospitals	66	31
Gender		
Male (%)	403 (59%)	146 (56.6%)
Female (%)	280 (41%)	112 (43.4%)
Age		
Median	3 years and 2 months	3 years and 6 months
Range	1 day—17 years and 11 months	13 days—17 years and 11 months

MCU, medium care unit; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

patients were drugs for the alimentary tract and metabolism and anti-infectives for systemic use.¹⁵

For 47 of all patients admitted to the SCH the reason for admission was an ADR (6.9%), 32 of these patients were exposed to cancer chemotherapy. For children admitted with a positive trigger score who used medication before admission, ADRs were the reason for admission in 18.2%.

ADRs in patients not exposed to cancer chemotherapy

From all patients who were not exposed to cancer chemotherapy, 15 were admitted due to an ADR (2.4%) (table 2). The ADRs in these patients were most commonly caused by vaccinations, anti-infectives for systemic use, immunomodulating agents and drugs for the nervous system.¹⁵ Patients with an ADR used an average of 4.7 drugs (95% CI 3.72 to 5.84), compared to 4.1 (95% CI 3.84 to 4.38) in children with a positive screening for the trigger list but without an ADR.

Two ADRs were medication errors, one caused by licensed drugs and one due to unlicensed used drugs. One case was a newborn, who was administered a 10-time higher doses of trimethoprim, the other case was excessive doses of valproic acid prescribed to a child with renal failure.

Table 2 Adverse drug reactions in patients not exposed to cancer chemotherapy

ATC*	Drug	Age†	Adverse drug event	Naranjo score‡	Avoidable?	Licensing state
A	Ranitidine	Newborn	Urticaria	6	No	Licensed
J	Amoxicilline	Baby/toddler	Vomiting	6	No	Licensed
J	DKTP/HIB vaccine	Baby/toddler	Dyspnoea	5	No	Licensed
J	DKTP/HIB vaccine	Baby/toddler	Fever, vomiting	6	No	Licensed
J	DKTP/HIB vaccine	Baby/toddler	Fever	6	No	Licensed
J	DKTP/HIB vaccine	Baby/toddler	Fever, refusal of food		No	
	Pneumococcal vaccine			4		Licensed
J	DKTP/HIB vaccine	Baby/toddler	Fever		No	
	Pneumococcal vaccine			4		Licensed
J	Tobramycin	Child	Haemorrhage	9	No	Unlicensed
J	Tobramycin	Child	Haemorrhage	10	No	Unlicensed
J	Trimethoprim	Newborn	Vomiting	6	Yes	Unlicensed
L	Infliximab	Child	Fever, tachycardia, abdominal pain	6	No	Licensed
L	Tacrolimus	Child	Vomiting	4	No	Licensed
L	Thymocytenoglobuline	Child	Serum sickness	6	No	Unlicensed
N	Lithium (transmission through placenta)	Newborn	Syncope	6	No	Unlicensed
N	Valproic acid	Child	Drowsiness	8	Yes	Licensed

*Anatomical Therapeutic Chemical (ATC) classification system of the WHO. A, alimentary tract and metabolism; C, cardiovascular system; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents N, nervous system.¹⁵

†Patient age by means of EMeA criteria: preterm, newborn (0–1 month), baby/toddler (1 month–2 years), child (2–11 years) and adolescent (12–18 years).

‡Probability measured by Naranjo score: ≤0 Adverse Drug Reactions (ADR) doubtful, 1–4 ADR possible, 5–8 ADR likely, ≥9 ADR certain.¹¹ DKTP, Difteria Pertussis Tetanus Polio vaccin; EMeA, European Medicines (Evaluation) Agency; HIB, Haemophilus Influenza B vaccin.

Adverse drug reaction-related admissions in paediatrics

Ten ADRs were caused by licensed prescribed drugs (67.7%) and five by unlicensed used drugs (33.3%). All cases were clinically mild. None resulted in permanent harm to the patient, significant haemodynamic instability or (in)directly to patient death.¹³ Both medication errors were avoidable, all other ADRs were not avoidable.

Patients exposed to cancer chemotherapy

From all 47 patients exposed to cancer chemotherapy, 32 were admitted due to an ADR (68.1%) (table 3). All ADR-related admissions were caused by chemotherapeutics (ATC code: anti-neoplastic and immunomodulating agents).¹⁵ Twenty-one patients (65.6%) were admitted for chemotherapy-induced neutropenic fever, of which 17 scored ≥ 9 for the Naranjo score. The licensing state of the prescribed drugs inducing neutropenic fever was determined as well. Two of these ADRs were caused by licensed prescribed drugs, two by unlicensed used medication and five by off-label used drugs. The other 12 neutropenic fever ADRs were caused by a combination of licensed, off-label and unlicensed used drugs. Table 3 lists the non-neutropenic fever ADRs found in patients exposed to cancer chemotherapy.

Of all ADRs in patients exposed to cancer chemotherapy, 5 were caused by licensed prescribed drugs (15.6%), 3 by unlicensed used drugs (9.4%), 8 by off-label used medication (25%) and 16 by combination of licensed, unlicensed and off-label used drugs (50%).

All ADRs in patients exposed to cancer chemotherapy were clinically mild, none of these resulted in permanent harm to the patient, significant haemodynamic instability or (in)directly to patient death.¹³ None of the ADR-related admissions in patients exposed to cancer chemotherapy were avoidable.

DISCUSSION

Overall, in this study, ADR-related hospital admission occurred in 6.9% of all acutely admitted paediatric patients, 2.4% in patients non-exposed and 68.1% in patients exposed to cancer chemotherapy. A study on ADR-related hospital admissions among adults in the Netherlands, including patients exposed to cancer chemotherapy, found a lower percentage of 5.6.⁵ In adults polypharmacy (the chronic use of five or more oral drugs) was one of the risk factors for an admission caused by an ADR.⁵ In children we could not demonstrate the same relation, although in our study patients with an ADR used an average of 4.7 drugs. The most common prescribed types of drugs causing ADEs in the adult population were platelet aggregation inhibitors, NSAID's and anticoagulants.⁵ In our study population we found no ADRs caused by these drugs, probably because antiplatelets and anticoagulants are rarely prescribed to the children. In contrast, vaccinations form a major cause of ADRs in our study population, whereas they are rarely prescribed to adult patients.

Table 3 Adverse drug events reactions in patients exposed to cancer chemotherapy, excluding neutropenic fever

ATC*	Drug	Age†	Adverse drug event	Naranjo score‡	Avoidable?	Licensing state
L	Methotrexate	Adolescent	Pancreatitis	4	No	Off-label
L	Vincristine	Adolescent	Constipation	7	No	Licensed
L	Vincristine	Child	Ataxia and diarrhoea	9	No	Licensed
L	Vincristine	Child	Ataxia and diarrhoea	10	No	Licensed
L	Asparagines			7	No	Licensed
L	Doxorubicin			7	No	Off-label
L	Vincristine	Adolescent	Retinal haemorrhage	7	No	Licensed
L	Carboplatin			9	No	Unlicensed
L	Etoposide	Child	Vomiting	9	No	Unlicensed
L	Cisplatin			9	No	Unlicensed
L	Dexrazoxaan			9	No	Off-label
L	Doxorubicin	Child	Anaemia	9	No	Unlicensed
L	Cytarabine		Trombopaenia, petechiae	9	No	Off-label
L	Mitoxantrone	Adolescent		9	No	Unlicensed
L	Cytarabine		Trombopaenia, petechiae	10	No	Off-label
L	Mitoxantrone	Adolescent		10	No	Unlicensed
L	Methotrexate			10	No	Off-label
L	Mercaptopurine			10	No	Off-label
L	Vincristine	Child	Leucopaenia	10	No	Off-label
L	Vincristine	Baby/toddler	Constipation	6	No	Off-label

*Anatomical Therapeutic Chemical (ATC) classification system of the WHO. A, alimentary tract and metabolism; C, cardiovascular system; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; N, nervous system.¹⁵

†Patient age by means of EMeA criteria: preterm, newborn (0–1 month), baby/toddler (1 month–2 years), child (2–11 years), adolescent (12–18 years).

‡Probability measured by Naranjo score: ≤ 0 Adverse Drug Reactions (ADR) doubtful, 1–4 ADR possible, 5–8 ADR likely, ≥ 9 ADR certain.¹¹ EMeA, European Medicines (Evaluation) Agency.

In our study, we also found that exposure to cancer chemotherapy is an important risk factor for the occurrence of ADRs. This result is also reported by Mitchell *et al*,⁷ who found 22% ADRs in paediatric oncology patients, compared to 2% in non-oncology patients. The high incidence of ADRs in patients exposed to cancer chemotherapy compared to non-exposed paediatric patients can be explained by the associated neutropenia.¹⁶ Neutropenic patients have an increased risk of infections.⁷ The fact that the percentage reported by Mitchell *et al* is much lower than the percentage found in our study is possibly attributable to the differences between the two studies. Mitchell *et al* included patients with both 'direct and referred admissions', whereas our study focused only on acutely admitted patients. Also the number of oncology patients included in our study was much smaller than in the study of Mitchell *et al*, being 47 in the first and 725 in the latter.

In our study all oncology cases were ADRs caused by antineoplastic and immunomodulating agents, no medication errors were found. None of the ADR-related admissions were due to drugs for supportive care. Mitchell *et al* describes that 94% of ADRs in these patients were caused by cancer chemotherapy, which is comparable to our results.⁷

The severity of ADRs in patients exposed to cancer chemotherapy was comparable with the severity of non-exposed patients. All ADRs were severe because of the hospital admission, but they were clinically mild, not resulting in permanent harm to the patient, significant hemodynamic instability or (in)directly to patient death.¹³

For patients not exposed to cancer chemotherapy comparable percentages of ADR-related admissions (0.59–4.1%) were found in other paediatric studies.^{7 17–20} Mitchell *et al*⁷ analysed 6546 admissions and found that 2% were caused by ADRs. The majority of these patients were 0–5 years of age.⁷ Another study conducted in Spain showed an incidence of 4.3% for patients in the same-age categories.¹⁸ McKenzie *et al*¹⁹ found an incidence of 2%, of which 37.8% were ADRs caused by chemotherapeutics. A meta-analysis on prospective studies found a weighted average of ADR-related admissions of 2.09%.⁶ Authors used different scoring systems for ADRs, none of the authors of the prospective studies used the Naranjo score. Furthermore, definition of ADRs and ADEs varies between studies.

According to the literature, a possible risk factor for the occurrence of adverse reactions in the paediatric population is the use of off-label and unlicensed used drugs. Horen *et al*⁸ found a relative risk of 3.44 (95% CI 1.26 to 9.38), for an ADR caused by off-label prescribed drugs in the out-patient clinic. Turner *et al*¹⁰ found that the use of unlicensed and off-label used drugs was associated with a 50% increase in ADRs in 936 paediatric inpatients. In our study no such relationship was found. An explanation for this could be the difference in population (acute admissions) and the relatively low number of ADRs as a reason for admission. In order to prove a

relation a larger number of patients or a case-control design is necessary.

A study in the Dutch adult population found that 46.6% of ADEs were possibly preventable.⁵ Studies in the paediatric population found similar percentages of 33–51.3%.^{20–22} In our study only 10% of ADRs was avoidable (table 2). Our data were based primarily on medical charts, possibly leading to missed signals that pointed towards an avoidable cause of the ADR. This may also explain our percentage of avoidable cases being lower than in the other studies. For example, Gallagher *et al* collected extra data through interviews with parents to get a better insight into medication use of children before admission.

Certain limitations to this study must be acknowledged. First, the trigger list might be incomplete. The trigger list has been based on experience in adult medicine concerning ADRs and was modified by expert experience to suit the paediatric setting. Second, the number of patients in this study was limited. This could have influenced the lack of significant results on the relation between ADRs and the licensing state of administered medication. Furthermore, the duration of drug use before admission and time of last dose prior to admission were not recorded. This may have been relevant for the likelihood of an ADR. Finally the results cannot be extrapolated to all other settings because the study was carried out at an academic institution. In conclusion, this study shows a relatively low percentage of ADR-related admissions in paediatric patients, with the exception of patients exposed to cancer chemotherapy.

CONCLUSION

In conclusion this study shows that ADRs occur more frequently in the paediatric population compared to adults, and more frequently in patients exposed to cancer chemotherapy. The ADRs that occurred were caused by vaccinations, anti-infectives for systemic use, antineoplastic and immunomodulating drugs and by medication for the nervous system. All ADRs in the paediatric wards and ICU as well as the oncology ward were relatively mild, none of the patients suffered permanent harm. No relation was found between the use of unlicensed and off-label use of drugs and the incidence of ADRs.

Contributors All authors have contributed equally to the design of the research method. Data collection was done by CWA and AGP. Analysis of the cases to determine potential ADRs was done by MdH, G'tJ, CMZ, LMH, BCMW and KvG. These authors assessed as well the licensing state, severity and preventability of the ADRs. Interpretation of the data was done by AGP, CWA and MdH who also wrote the first draft of the article. Critical revision and rewriting were done by G'tJ, CMZ, LMH, BCMW and KvG.

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Competing interests None.

Adverse drug reaction-related admissions in paediatrics

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